Cyclo-oxygenase inhibitors of human diseases

Historical background

Cyclooxygenase (COX) inhibitors are a widely prescribed group of antipyretics and analgesics worldwide and are important component in the treatment of inflammatory conditions. Although first COX inhibitor was discovered more than a decade ago their origin dates back to ancient Mediterranean descent1. Back and other body pains where treated using extracts of poplar tree bark and leaves of myrtle. Use of willow bark emerged far more lately and its first appearance was reported in England in 17631. As was later discovered, the essence of the willow bark possessing anti-inflammatory and antipyretic properties was salicin. Further modification of its structural properties allowed generation of salicylic acid that eventually was developed via Kolbe reaction using phenol1, 3. In 1899 Bayer company went ahead in synthesising more susceptible derivative of it, acetylsalicylic acid and named it aspirin. Following this phenylbutazone (1949) and indomethacin (1963) came along however the mystery of mechanism of their action in the body was not yet developed. It was not known until 8 years later when an idea surrounding the synthesis of prostaglandins within body was revealed and for which a Nobel Prize in physiology and medicine was awarded (1982)1. It was proposed that first non-steroidal anti-inflammatory drug (NSAID), aspirin, acted upon inhibition of an enzyme that played role in utilising unsaturated fatty acids into biochemical molecules exerting their action in conditions such as inflammation, pain, and fever and platelet synthesis. It was accepted that during changes occurring within stimulated cells and tissues prostaglandins synthesis was taking place 1, 3. Structure of COX was isolated in 1976 and its second isoform was confirmed around 14 years later by few different laboratory investigations; investigations which

greatly allowed appreciating the nature of first nonselective cox inhibitors – NSAIDs – in the treatment of human diseases1.

1. 1 The pharmacology and chemistry of cyclooxygenase enzyme

Cyclooxygenase (COX aka PGG2/H2 synthase) belongs to the family of enzymes known as myeloperoxidases and it is the crucial enzyme in the synthesis of prostaglandins, prostacyclin and tromboxane A2 resullting from the conversion of arachidonic acid (AA) 2, 4. This heme-containing COX enzyme is a bifunctional biocatalyst with two interconnected active sites: cyclooxygenase and peroxidase which action involves generation of hydroperoxy endoperoxide – PGG2 via cyclooxygenase cycle (Fig. 1.) into its reduced form of hydroxy endoperoxide (PGH2) (Fig. 2.) 2, 4. Both isoforms of COX enzyme are expressed in endothelial, monocytic and renal cells with COX-2 being more profound in inflammatory and cancer tissues. Both enzymes are characterised by signal peptide, endothelium growth like factor (EGF) region, membrane in-bound domain, catalytic part, interface between monomers and N-linked polysaccharides residues2.

The signal peptide in COX-1 consists of 23 residues whereas COX-2 has only 17. The EGF like region constitutes a major part of the interface and is not found in other myeloperoxidases. It is involved in Cys-Cys cross linked bridges with lack of Cys9 in COX-1 and Cys512 in COX-2. The membrane in-bound domain accounts for 33% of overall similarity and 24% of identity within membranous face. This domain is described as consisting of 4 amphipathic a helices that surround the entry to the COX site. The catalytic part is known to be the largest part of the enzyme with remained homology between other myeloperoxidases. 180° rotation between subunits is

preserved with chemical interaction between polar, ionic and hydrophobic moieties. Differences in residue positioning prevent heterodimerization and dissociation from facial interaction inactivates the enzyme’s overall catalytic activity 1, 2, 3, 4, 5.

Figure 1. Mechanism of COX cycle in cyclooxygenase active site showing free radicals formation denoted by ? prior to PGH2 synthesis in POX pathway (not shown) 2. Attraction of hydrogen atom from Tyr385 by peroxyl radical of PGG2 allows for the regeneration of the steps of the reaction in the COX cycle of prostanoid biosynthesis. The coloured boxes are to indicate the origin of oxygen atoms. PLA2 – phospholipase A2, S – secretory, C – cytoplasmic.

Figure 2. A diagram summarising changes made to AA in the distinct active sites of the PGG2/H2 synthase and products formed via action of each catalytic active site 2.

1. 2 The nature of cyclooxygenase inhibition in the human body

Inhibition of cyclooxygenase action is desired in the treatment of human diseases. Not only because it suppresses the inflammatory production of prostaglandins in the conditions such as: dysmenorrhoea, rheumatoid arthritis, osteoarthritis but also because it prevents platelet aggregation, suppresses tumour growth and prevents cancer5. Until 1994 it was not clear by which mode, mechanism or process inhibition of COX was carried out. Just complexation studies between COX and flurbiprofen allowed insight into molecular basis of COX inhibition. The investigation led by Garavito and his colleagues proposed such model of inhibition. In his model it was suggested

that the enzyme in question possesses long hydrophobic path that originates from in-membrane bound moiety up to the heart of the dimer subunit. Blocking this channel stops the endogenous substrate (AA) from binding hence possible intervention in the process of prostaglandins biosynthesis5.

1. 3 The types of cyclooxygenase inhibitors in the treatment of human diseases

There are several types of COX inhibitors available in the treatment of human diseases. The very first one, aspirin, is known to act through non-selective and irreversible manner. As this manner suggests aspirin binds to both types of COX enzyme by acetylating Ser530 residue upon covalent modification. Consequently effects such as risk of excessive bleeding, ulcer formation or foetal deformation limit the use of aspirin in dealing with long term diseases. Nowadays it is mainly considered as the important component in the treatment of cardiovascular conditions due to its anti-platelet activity 1, 3.

Other types of non-selective NSAIDs such as piroxicam, ibuprofen or diclofenac, constitute majority of therapeutic agents being prescribed however due to harmful effects they are being considered less effective in the long term treatment. The damage to the gastrointestinal (GI) system is due to inhibition of COX-1 expressed in GI mucosa which results in formation of ulcers with associated bleeding. Therefore since the main target for choosing those drugs is found to be of inflammatory nature (inhibition of COX-2) they are nowadays preferred in topical dosage forms 1, 3, 5.

The consequence of the undesired effects caused by non-selective COX inhibitors targeted new approach towards development of more specifically

acting agents. The era began on discovery of the second isoform of cyclooxygenase and introduction of first COX-2 selective agent (1999) was introduced to the market within 10 years since its discovery with celecoxib and rofecoxib for the treatment of arthritis. The discovery proposed mechanism of actions of both enzymes within the body with COX-1 possessing more constitutive effects especially in GI tract. It was therefore suggested that COX-2 was an inducible form in conditions such as inflammation and pain, symptoms desired in treatment of human diseases associated with the effects of COX-2 isozyme 1, 3.

2. ASPIRIN – THE ORIGINAL COX INHIBITOR (Joyce)

2. 1. Pharmacology and chemistry of Aspirin

Plant ingredient salicin was discovered in the willow bark and leaves in the 17th century by a greek physician (Hippocrates) who prescribed it as an analgesic and antipyretic.

Further into the 17th century a crude form of salicylic acid was made by a German scientist (Charles Frederic von Gerhardt). This was followed by production of a purer form of salicylic acid by another German chemist (Karl Johann Kraut). Finally in 1897 a German chemist Felix Hoffmann, who worked for the pharmaceutical company Bayer, was assigned the task to find a better derivative of salicylic acid. He also had his own personal reasons for wanting to find a better derivative. His father had been taking salicylic acid for his arthritis pain but could no longer take it without vomiting3, 7. In 1889 Hoff man then found a way of acetylating the hydroxyl group on the benzene ring of salicylic acid to form acetylsalicylic acid. Hoffman father tried the new

derivative and it was pronounced effective. The name ‘ ASPIRIN’ was given to the drug by Bayer chief pharmacologist Henrich Dreser7.

Aspirin was found to have antipyretic, analgesic and anti-inflammatory effects. It does this by inhibiting cyclo-oxygenase(COX) or prostaglandin endoperoxide synthase(PGHS) enzyme irreversibly. COX is responsible for cyclizing arachidonic acid and adds the 15-hydroperoxy group to form PGG2 which is the precursor to prostaglandins. An enzyme perioxidase is responsible for reducing the hydroperoxy group of PGG2 to the hydroxyl group of PGH2.(4)(See Figure 15- prostaglandins synthesis)

Prostaglandins can be described as chemical mediators that produce a variety of strong physiological effects in the body. Most importantly they are responsible for the activation of the inflammatory response, production of pain, and fever.

There are three isoforms of the COX enzyme of which aspirin has an effect on two which are COX-1 and COX-2. Aspirin binds covalently modifiying COX-1 through acetylation of its Ser-530 and COX-2 through acetylation of its serine 516 residue by placing a bulky constituent (acetyl) and this directly inhibits binding of arachidonic acid. Aspirin’s action is more potent against COX-1 than against COX-2. This difference in inhibition of the two COX enzymes by aspirin is due to the larger volume of the COX-2 active site produced by the Val-523 substitution at the side pocket. (1, 7, 9)

The difference in the size of the active site has been exploited by pharmaceutical companies to develop selective COX-2 inhibitors (section 4)

COX-1 is an essential enzyme expressed in majority of tissues and also in platelets. It is responsible for prostaglandin production involved in homeostatic mechanisms e. g. platelet aggregation, gastric wall protection, regulation of renal blood flow and initiation of labour in childbirth. In contrast, COX-2, is an inducible form which becomes up regulated by inflammatory mediators such as cytokine (Interleukin and tumour necrosis factor).

2. 2 The problems associated with aspirin(1, 10)

a. Unwanted effects

1. GASTRIC PROBLEMS
2. The inhibition of COX 1 can produce gastric disturbances as an unwanted effect because the prostaglandin production in the GI tract is a homeostatic mechanism to protect the gastric mucosa. It causes inherent symptoms like heartburn; dyspepsia, nausea, and abdominal pain. (1, 10)This effect can cause Aspirin users to change or discontinue it’s use. Some of these inherent symptoms are quite common for most NSAIDs. Secondly it can also causes gastro duodenal mucosal lesions such as erosions and asymptomatic ulcers, which may or may not heal spontaneously; and finally more serious gastro ulcers with life-threatening complications like perforation, symptomatic ulcers, and bleeding ulcers. Symptoms of this could be black, bloody, or tar like stools or vomiting/coughing up blood
3. REYE’S SYNDROME
4. Reye’s syndrome is a collection of symptoms consisting of altered consciousness, convulsions, low blood glucose, and enlargement of the

liver associated with fatty infiltration of the liver. It is a deadly disease, which can strike any child, teenager, or adult without warning. All body organs are normally affected, but the liver and brain are antagonised the most.

In 1965 it was stipulated that Reyes's syndrome can be caused by the administration of aspirin in children under 16years of age. There is no discovered mechanism for the role of salicylate in this but it is thought that aspirin enhances the release of tumour necrosis factor which induces apoptosis of cells which can cause inflammation, viral replication e. t. c.

5. SALICYLISM
6. This is caused by the excessive ingestion of aspirin. There are two main pathways in the metabolism of aspirin. (10)Phase 1 reaction that involves the oxidation of aspirin to salicylic acid by a cytochrome P450 monooxygenase. By addition of a reactive group (OH) to get it ready for conjugation to a soluble component and hence aid excretion. This conjugation involves the attachment of small polar molecules glycine and gluconoride to salicylic acid. This results in further deactivation of the aspirin and the production of water-soluble metabolites that will be readily excreted in the urine or bile. The pathway conjugated with glycine, is the one that is easily overloaded in cases of toxicity. Thus elimination of salicylic acid slows down and accumulation leads to a variety of side effects. Below are the pathways showing oxidation and conjugation.

This excess salicylate produces toxic effects include below.

1. Ringing in ears

2. Hyperventilation which causes increase in CO2- respiratory alkalosis,
3. Dehydration: increased water loss due to hyperventilation
4. Loss of carbonic acid – metabolic acidosis. This in turn will reduce the blood pH, and make aspirin return to its non-ionised form allowing free aspirin in the blood stream.
5. Hyperthermia. These pathways overload uncouples the energy producing processes (oxidative phosphorylation) of the mitochondria thus causing production of heat rather than ATP.
6. Fatality especially in children

Interactions with other drugs

- Reduced effect of aspirin if given with ibuprofen and avoid concomitant use of aspirin with NSAIDS due to increased side effects.
- Increase risk of bleeding when aspirin is given with coumarins, SSRIs, clopidogrel, illoprost, and sibutramine,
- Aspirin enhances effect of Heparins, Phenytoin, Valporate,
- Aspirin antagonises effect of Spirolactone, Sulfinpyrazone and Probenacid
- Rate of excretion of aspirin is increases by some antacids.
- The effect of aspirin on the gastrointestinal tract may be enhanced by the intake of alcohol and corticosteroids.

3. NON STEROIDAL ANTINFLAMMATORY DRUGS – NON SELECTIVE COX INHIBITORS (Christina)

3. 1 Isozymes of Cyclooxygenase

Cyclooxygenase has various isozymes. The main isozymes are COX-1 and COX-2, however there is now evidence of a third form- COX-3.

COX, originally known as prostaglandin H synthase is responsible for the oxidation of arachadonic acid to prostaglandin G2 and prostaglandin H2. It catalyses the reaction in which the arachadonic acid substrate and two molecules of O2 are converted to prostaglandin G2 and then in the perioxidase reaction Prostaglandin G2 is reduced to PGH2 by a 2 electron reduction.

The COX isozymes are heme containing enzymes that are homodimers. Each monomer contains three main domains; A membrane binding domain, a N-terminal epidermal growth factor domain and a C-terminal catalytic domain. COX-1 is made up of 602 amino acids while COX-2 is comprised of 604. 3

The catalytic reaction in COX takes place in a hydrophobic channel in the core of the enzyme while the peroxidise reaction takes place in the heme containing region near the surface of the enzyme. The membrane binding domain consists of four alpha helices with one helix that fuses with the catalytic domain. These helices congregate around an opening and through these openings fatty acids and NSAIDS are considered to enter the active site. The COX-1 isozyme is considered a constitutive enzyme. It is present in high volumes in most cells and tissues i. e. renal collecting tubules, monocytes, endothelium etc. However COX-2 is hardly noticeable in most cells, it is an inducible enzyme so it becomes more abundant in cells or tissues when macrophages are activated or by any other inflammation mediators e. g. TNF-a (tumor necrosis factor-alpha) or IL-1 (interleukin-1). 5

Both COX-1 and COX-2 isozymes are attatched to the endoplasmic reticulum and nuclear envelope. The COX isozymes need to be N-linked glycosylated to

enable them to be folded and attatched to the endoplasmic reticulum and nuclear envelope. The COX isozymes have very similar structures for their binding site, catalytic mechanisms and produce the same biosynthetic products3

COX-3

COX-3 a third isozyme was discovered in 2002 by Simmons and co-workers. They conducted a study on dogs and this resulted in them discovering a novel COX-1 splice variant termed COX-3 that was sensitive to acetaminophen (paracetamol). It was suspected for a while that acetaminophen worked by inhibiting a different specific isozyme due to the fact that it did not directly inhibit COX-1 and COX-2 very effectively at therapeutic concentrations but it generated prostanoids in neuronal systems. 3, 15

The Simmons and co-worker group showed that acetaminophen was the actual target for COX-3, and that it acted separately from COX-1 and COX-2. 3

Canine COX-3 is a membrane bound protein consisting of 613 amino acids with a molecular weight of ~65 kDa. It has a high expression in cells and tissues like COX-1 suggesting it may be a constitutive enzyme. However the question that needs to be asked is if generalisations can truly be made on the presence of COX-3 in humans based on Canine studies, so future experiments need to be designed to clarify whether a human COX-3 actually does exist that acts independently from COX-1 and COX-2 in vivo. 14

NSAIDs are known to inhibit COX in order for them to exhibit their anti-inflammatory actions, a structural NSAID binding study was carried out.

The COX-1 active site contains a long hydrophobic channel that extends from the membrane binding domain to the core of the COX monomer. The tip of the COX active site houses Tyr385 that is located near the heme iron. Ser530 is positioned just below Tyr385 and that is the site for aspirin acetylation. Glu524 and Arg120 are positioned at the mouth of the COX-1 channel. A typical NSAID such as fluobriprofen, when introduced to the COX enzyme, its carboxylate moiety is usually directed towards the mouth of the COX-1 channel in order for it to be positioned in the most ideal place that will allow it to interact with the two polar residues Glu524 and Arg120. From these studies a better insight into the binding profiles of NSAIDs were observed.

Non selective NSAIDs can bind in three different ways:

- Reversibly (e. g. Ibuprofen)
- Fast, low affinity reversible binding followed by a higher affinity, time dependant slowly reversible binding (e. g. fluobriprofen)
- Rapid, reversible binding followed by a covalent modification of the enzyme (e. g. Aspirin) 3

Arg120, Glu524, Tyr355 and His90 form a network of hydrogen bonds at the entrance of the COX channel acting like a gate to the binding site. NSAIDs generally bind between the upper portion of the COX channel near Tyr 385 and Arg 120 which is at the mouth of the COX channel. 3

Through the use of hydrogen bonding and electrostatic interactions, the carboxyl moiety of acidic NSAIDs like fluoribiprofen interact with Arg120 in

both COX isozymes. The significant differences in the structure of the binding sites for both COX isozymes has been manipulated to enable the design of selective COX-2 inhibitors.

In the COX-2 active site there is an extra accessible pocket due to the presence of a smaller valine amino acid residue at position 523 and a valine substitution at position 434, unlike COX-1, this difference increases the overall volume at the COX-2 active site by about 20%. 1 This means that due to reduced steric and ionic crowding at the mouth of the channel by Arg120, non acidic selective COX-2 inhibitors can show an enhanced and specific binding to the COX-2 enzyme. Another structural difference exists at the amino acid residue 513 where COX-1 has a histidine residue and COX-2 has an arginine moiety. 1 These small differences provides flexibility in the substrates that can be utilised in the COX-2 active site.

3. 2 Problems Associated With Non Selective Non Steroidal Anti-Inflammatory Drugs

NSAIDs are one group of drugs that are regularly used by the world’s population to relieve pain, reduce inflammation and lower temperature. They are COX inhibitors and act to inhibit the catalysation of arachadonic acid to PGH2. COX-1 is constitutively present in most cells while COX-2 is induced by chemical mediators of inflammation and activated macrophages. 13

COX-1 and COX-2 as mentioned above have 2 specific roles. The 1st role gives PGG2 and the other role is in the peroxidise reaction that gives PGH2. Both COX-1 and COX-2 inhibitors work by inhibiting the 1st and main role i. e. inhibiting the conversion of arachadonic acid to PGG2. COX-1 and COX-2 possesses hydrophobic channels within their core. The classical NSAIDs

exhibit their effects by blocking these enzymes halfway down the COX channel near Tyr385 and the Arg120 which is at the mouth of the COX channel by hydrogen bonding to the Arg120 residue. This results in the prohibition of any fatty acid substrates from entering the catalytic domain of the COX enzyme. 3

In COX-1, these drugs tend to inhibit the enzyme quickly yet generally the inhibition is often reversible, however in COX-2 the inhibition is time dependant and often results in irreversible inhibition.

As mentioned before, the COX-1 and COX-2 isozyme differ slightly. In the COX-2 active site there is an extra accessible side pocket due to the presence of a smaller valine amino acid residue at position 523 instead of isoleucin as in COX-1. This is important for understanding why some NSAIDs are selective for the COX-2 isozyme. 13

There are a number of side effects associated with traditional NSAID therapy. NSAIDs can cause renal failure, liver damage/disorders, aseptic meningitis, skin reactions and bone marrow disturbances which can interfere with bone fracture healing. However amongst them all gastrointestinal (GI) toxicities is amongst the most common. These are believed to arise from the inhibition of COX-1 in the gastric mucosa. 14

GI toxicities

In humans and other species it has been shown that COX-1 not COX-2 is constitutively expressed throughout the GI tract. 13 COX-1 is responsible for the synthesis of prostaglandins like PGE2 and PGI2 which are responsible for protecting the GI mucosa by reducing acid secretion in the stomach by the

parietal cells, increasing blood flow in the mucosa and stimulating the release of viscous mucous. This leads to conditions of ulcers, dyspepsia, diarrhoea, nausea and vomiting and can even lead to gastric bleeding in some cases.

These undesirable side effects have led to the development of COX-2 selective inhibitors.

These drugs are effective anti-inflammatory's and reflect good analgesic effects. They have considerable less gastric damage due to the fact they selectively inhibit COX-2 with minimal action on COX-1.

Unfortunately the use of COX-2 selective drugs has been associated with increased incidence of myocardial infarction and stroke. 3

Renal effects

Prostaglandins especially PGE2 and PGI2 are involved in regulating renal blood flow and vascular tone. Recent studies have shown that COX-2 is constitutively expressed in the macula densa, epithelia cells lining the ascending loop of henle and medullary interstitial cells of the renal papillae, while COX-1 is constitutively expressed in the collecting ducts, loop of henle and in the vasculature. The COX-2 enzyme is associated with normal renal function and inhibition of COX-2 results in NSAID-induced sodium retention while inhibition of COX-1 results in a disease in glomerular filtration rate. 3

This conclusively tells us that both COX-1 and COX-2 are involved in the physiology of the kidneys. However therapeutic doses in patients with normal renal function are at little risk of renal complications. It is mostly

neonates and the elderly who are more susceptible as well as patients with heart, liver or kidney disease.

4. SELECTIVE COX 2 INHIBITORS (Nadine)

4. 1 Reasoning behind selective inhibition

4. 2 Benefits and risks

5. MECHANISM OF ACTION OF COX INHIBITORS IN HUMAN DISEASES

5. 1 Analgesic (Joyce)

Pain can be defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Pain is a self protection mechanism which helps of forces us to identify danger and move away from it. It is one of the main symptoms used to identify a condition in medicine.

Removing pain is very essential in terms of either eliminating the disease or condition or in fact suppressing its effect. This can be done by the use of medicines called analgesics.

Pain receptors also called nociceptors are present on special nerve fibres that are sensitive to noxious of harmless stimuli. The stimulation of these receptors are on A-delta and C-fibers which are located in skin, connective tissue, viscera, muscle e. t. c. COX inhibitors act by blocking transmission to peripheral nerves.

Pain associated with

I. Arthritis

Arthritis is the inflammation of joints. The inflammation and movement of the joints cause extreme pain in the sufferer. There are two major types

a. Osteoarthritis(10)

This is a chronic disease that features the breakdown of the joint's cartilage. Cartilage is flexible connective tissue found in between joints that cushions or protects the ends of the bones and allows easy mobility of joints. This breakdown of cartilage causes the bones to rub against each other creating friction, causing joint tension, pain and loss of mobility in the joint. There are different types of arthritis of which osteoarthritis is most common; it can also be referred to a degenerative joint disease. There are two types of osteoarthritis, primary of which is associated with old age, general wear and tear of the cartilage. And secondary where it occurs where there is a cause example obesity, trauma, or hereditary.

Treatment: Paracetamol may be considered as first line therapy for Osteoarthritis patients with mild to moderate pain. If the pain does not respond to paracetamol or patient has severe symptoms then other traditional NSAIDs like Ibuprofen, diclofenac or coxibs should be used. Coxibs have shown to produce reduced GI side effects. However they have the probability of increasing cardiovascular risk because they inhibit prostacyclin production in endothelial cells but not thromboxane in platelets, hence this can increase the chance of a thrombus formation. The choice of a coxib or a specific NSAID should be based on the patient characteristics and risk factors.

b. Rheumatoid arthritis(12)

This is an autoimmune disease of unknown origin whose major characteristic is the inflammation and erosion of the synovial membrane or synovium. This membrane lines and surrounds the joint and synovial cavity. The synovium

secretes a slightly viscous, clear fluid known as synovial fluid, which lubricates cavity that lies between the cartilage and joint on the bone.

In Rheumatoid arthritis accumulation of the synovial fluid builds up within the joint space and causes inflammation. This makes the joint look and feel swollen. Rubor occurs do to the increased blood flow to the area because of inflammation. In conditions of long-term RA, joint degeneration can occur causing mobility to be very painful and restricted.

Treatment: Aspirin used to be used to treat RA but because of its GI toxicity. The use of aspirin as first line of therapy has been superceded by other NSAIDs. There are a large number of NSAIDs that have been invented since aspirin, but have similarities in toxicities e. g. Ibuprofen, naproxen meloxicam, etodolac selective COX-2 inhibitors have been invented to control inflammation. These drugs were designed to combat the gastrointestinal risk of NSAIDS, but there are concerns of increases in cardiovascular risk.

II. Cancer (11)

Can be defined as an abnormal growth of cells as when a group ofcellsdisplayuncontrolled division, invasion, and sometimesmetastasis. Cells become cancer cells because of its damaging effect to the DNA of the cell. A normal cell will try to repair damaged DNA but in a cancer cell it replicates with the damaged DNA. The cancer cell continues making new cells that the body does not require.

The most common cause of cancer pain is infiltration of the tumour into bone. Bone metastases occur as a consequence of different types of cancer.

Another mechanism of pain apart from bone metastasis is the secretion of Prostaglandins by carcinomas.

For this reason, NSAIDs should be included in any regimen to control pain associated with bone metastasis.

Because NSAIDs do not activate opioid receptors, they can provide additional pain relief when combined with an opioid analgesic. Thus, combining an NSAID with an opioid analgesic may provide adequate pain control with a clinically significant reduction in opioid dose. This opioid-sparing effect of NSAID therapy allows the clinician to diminish the side effects associated with opioid therapy without sacrificing pain control.

Coxibs: Another Option for Cancer Pain Management(11)

The recent introduction of the coxibs, on their use in cancer patients is still being studied. Oncologists are replacing NSAIDs, with the use of coxib, because of the improved safety profile compared to traditional agents. Surgical oncologists are exploring the use of coxibs both preoperatively and during the post-operative period to reduce opioid usage in order to speed the recovery process

5. 2 – Anti-pyretic (Nadine)

5. 3 – Anti-inflammatory (Christina)

To date there are over 100 inflammatory diseases- each of which causes the degeneration of connective tissue in one or more parts of the body. These include:

Rheumatoid Arthritis

Osteoarthritis

Atherosclerosis

Irritable Bowel Disease

Alzheimers and many more.

Inflammation is characterised by dolor, rubor, calor and tubor, it’s one of the body’s ways of responding to harmful stimuli, pathogens, injury or disease. These usually initiate an acute or chronic inflammatory response.

Arthritis is a general term used to characterise inflammation in the joints. Rheumatoid arthritis describes arthritis that occurs on both sides of the body i. e symmetrical. These usually occur in the wrists, hands and knees. It is not known what causes this disease many theories have been put forward but it happens when the immune system begins to attack the joints.

A number of anti-inflammatory drugs are available worldwide and are widely used to relieve pain, swelling and inflammation associated with soft tissue inflammation. A number of these drugs act via the inhibition of COX.

When you experience pain and inflammation from arthritis, an increase in microvascular permeability occurs selectively in post-capillary venules. The endothelial cells undergo conformational change leading to vascular leakage through gaps between the adjacent endothelial cells. At the site of injury phagocytes are attracted and move into the affected tissue along with plasma. The plasma causes the associated swelling observed in inflammation and the phagocytes engulf dead cells and bacteria.

Prostanoic acids are